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(19)

(54) TABLET FORMULATIONS

(71) We, SANDOZ LTD., of 35 Lichstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to medicament formulations.

More particularly, it relates to medicament formulations comprising Griseofulvin/polyethylene glycol.

Griseofulvin is an antifungal agent which is preferably administered orally in the form of tablets. However, because the drug has poor water solubility and a low dissolution rate, such tablets may not exhibit satisfactory drug release.

Griseofulvin has been reduced in a particle size (micronized) with a significant improvement in the dissolution rate, and this improvement has been utilized commercially in tablet formulations. It is also known, that a solid dispersion of Griseofulvin in polyethylene glycol exhibits an improved dissolution rate over the micronized form of Griseofulvin. However, when the Griseofulvin/polyethylene glycol solid dispersions are formulated into tablets much of the improvement in dissolution rate is lost. It is believed that compression of the formulation during tabletting results in significant bonding due to the polyethylene glycol's strong cohesive forces, which forces must be overcome in the aqueous gastric fluids in order to release the discrete particles of drug in the formulation.

Conventional disintegrating agents, for example corn starch and alginic acid are found to be inadequate when used with Griseofulvin/polyethylene glycol tablet formulations.

According to the present invention, there is provided a medicinal tablet comprising a solid dispersion of Griseofulvin in polyethylene glycol and from 18 to 99 percent by weight of the tablet of crosslinked polyvinylpolypyrrolidone as a disintegrating aid.

The term 'tablet' is here understood to mean any coherent, compressed, solid formulation, irrespective of its shape or dimensions.

The crosslinked polyvinylpolypyrrolidone (PVPP) is an insoluble polymer of N-vinylpyrrolidone, which may be prepared by heating N-vinylpyrrolidone in the presence of a small amount of alkali metal, or alkaline earth metal, or the oxides, hydroxides, or alkoxides of these metals, as disclosed in U.S. Patent No. 2,938,017. The cross-linked polyvinylpolypyrrolidone thus formed is insoluble in water, strong mineral acids, caustic solutions, and common organic solvents, but is wettable by, swellable in water. A suitable material is available commercially from GAF Corporation under the name POLYCLAR AT (Registered Trade Mark). POLYCLAR AT is a food-grade poly(vinylpolypyrrolidone) prepared by the process of U.S. Patent 2,938,017 and sold as a clarifying agent for beers and wines. It is an off-white free-flowing powder with 5.0% maximum water content and 50ppm. maximum soluble PVP. It contains less than 20ppm heavy metals and less than 2ppm arsenic. It is to be distinguished from uncrosslinked polyvinylpyrrolidone (PVP), which is water-soluble.

The solid dispersion of Griseofulvin in polyethylene glycol may be prepared by dissolving Griseofulvin (in micronized or normal particulate form) in hot molten polyethylene glycol, of molecular weight in the range 4000 to 6000, shock-cooling the resulting solution and reducing the resulting solid dispersion to a convenient particle size. The Griseofulvin may constitute from 2% to 50% by weight of the resulting Griseofulvin/polyethylene glycol, preferably from 20% to 30%.

The tablets of the present invention may contain from 18 to 99 percent by weight of PVPP, preferably 18 to 25% by weight, more preferably 20 to 25% by weight. The tablets may also contain, in addition to Griseofulvin/polyethylene glycol and PVPP, standard pharmaceutical tablet excipients

for example lactose, magnesium stearate, stearic acid, talc, gelatin, tragacanth, lecithin and calcium carbonate. The tablets may be uncoated or may be coated in conventional manner.

The tablets can be prepared using conventional commercial wet and dry tabletting techniques. A suitable procedure in dry tabletting is, for example, as follows: the drug, tablet diluent, e.g. lactose U.S.P. and disintegrant are passed through a screen, such as a 20 mesh stainless steel screen and then transferred to a twin shell blender and blended for about 10 to 20 minutes. The tablet lubricant e.g., magnesium stearate or silicon dioxide is passed through a cloth such as a No. 60 mesh cloth and then transferred to the blender. Mixing is then continued for an additional 5 to 15 minutes. After mixing, the resulting granulation is compressed into tablets to a hardness of about 7 to 13 kg., depending upon the ultimate use of the tablet cores, e.g., for coated or uncoated tablets.

In wet tabletting, a suitable procedure is, for example, as follows: the drug, diluent and disintegrant are passed through a screen such as a 20 mesh stainless steel screen and then transferred to a blender, and blended for about 10 to 20 minutes. The blended mixture is then granulated with a binder in a hydroalcoholic or aqueous solution to a suitable wetness. The wet granulation is passed through a screen such as 14 mesh stainless steel screen and then dried at 45°C. to loss on drying (L.O.D.) of 1 percent to 3 percent. The dried granulation is again passed through a screen The tablet lubricant, e.g., magnesium stearate or silicon dioxide is passed through a cloth, such as a No. 60 mesh cloth, added to the granulation and the resulting mixture is transferred to a twin shell bender and blended for about 5 to 15 minutes. The resulting mixture is compressed into tablets on a tabletting press to a hardness of about 7 to 13kg, depending upon the ultimate use of the tablet cores, e.g., for coated or uncoated tablets.

The screen and cloth size mentioned herein are standard US Series Sieve sizes: see, for example, US Pharmacopeia, XVIII edition, page 940.

The following Examples and comparative Examples illustrate the invention:

Examples 1—2 and Comparative Examples 3—7

I Preparation of tablet formulations

The tablet compositions of Table I (below) were prepared by the following dry tabletting procedure:

1) Griseofulvin and polyethylene glycol 6000 was heated to form a solution containing 25% by weight Griseofulvin, and then rapidly cooled to form a solid dispersion.

2) The solid dispersion was milled to obtain fine granules.

3) The Griseofulvin/polyethylene glycol, spray-dried lactose and disintegrant were each passed through a No. 20 mesh stainless steel screen, transferred to a twin shell blender and mixed for 15 minutes.

4) The magnesium stearate and colloidal silicon dioxide was passed through a No. 60 mesh cloth, added to the blender and mixing contained for an additional 5 to 10 minutes.

5) Tablets were compressed from the mix, with a weight of 900 mg, and a hardness of 13 to 15 kg, using a Colton Model 204 tablet press equipped with 19 mm elliptical punches.

All formulations (900 mg tablets) contained 500 mg 25% Griseofulvin/polyethylene glycol, 9 mg magnesium stearate and 9 mg colloidal silicon dioxide. The remaining ingredients are shown in Table I.

TABLE I

Example No.	wt. Lactose (mg)	disintegrant	wt. disintegrant (mg)	% by wt. disintegrant
1	202	PVPP	180	20
2	230	PVPP	162	18
3	247	PVPP	135	15
4	283	PVPP	99	11
5	202	alginic acid	180	20
6	112	alginic acid	270	30
7	292	corn starch	90	10*

*a greater quantity of corn starch gave unacceptable tablet properties.

II Disintegration times

Disintegration times shown in Table II for the tablets prepared from the formulations of Table I were determined using the United States Pharmacopeia XVIII (p. 932—933) test procedure for uncoated tablets. Each disintegration time result is an average of three tests.

TABLE II

Example No.	% distintegrant by wt.	disintegration time (minutes)
1	20	4 – 6
2	18	4 – 7
3	15	13 – 15
4	11	20 – 26
5	20	50 – 60
6	30	50 – 60
7	10	>120

It is seen that the disintegration times of formulations 1—4, using PVPP as disintegrant, are superior to those of formulations 5—7, using alginic acid and corn starch, and that the disintegration times of formulations 1 and 2 according to the present invention, containing 18% or more PVPP are superior to those of formulations 3 and 4, containing less than 18% PVPP.

III Dissolution rate studies

Dissolution rates were measured on the tablets of Examples 1—6 (PVPP and alginic acid as disintegrants). The dissolution rate gives an indication of drug availability. The following procedure was used:

MEDIUM: Distilled Water

APPARATUS: The test is conducted directly in a glass cylindrical tank, capacity slightly above 23 l. A heating element is immersed in the bath and connected to a contact thermometer and appropriate temperature control relay. Three types of stirring elements are used simultaneously.

a. A circulating pump and a Tygon tube is attached to the outlet and the other end is attached by a clamp so that the tube makes a semicircle clockwise to a point 180° from the pump and near the bottom. The direction of flow from the pump is thus clockwise and from the top of the tank to the bottom at a point on the opposite side of the tank. The flow rate is about 1600 ml per minute.

b. The tablet is placed in a U.S.P. XVIII basket, which is rotated clockwise at 100 rpm at a distance of 7.5 cm from the bottom of the basket to the bottom of the tank.

c. A stirrer apparatus is rotated clockwise at 180 rpm. It is set up so that there are four sets of stirring blades on one shaft. The stirrer bottom is placed 1 cm from the bottom of the tank.

All three stirrer systems are located in one-half of the tank. In clockwise order, they are the circulating pump, the U.S.P. basket, the stirrer shaft, and the outlet from the circulating pump's hose connection. There is an interval of approximately 12.5 cm between each piece of equipment. The two stirring shafts are 9 to 10 cm from the side wall. The hose outlet is about 5 cm from the wall.

PROCEDURE: 24 l of distilled water is placed in the tank. The temperature is allowed to equilibrate at 37 ± 0.5°C. The pump and paddle stirrers are turned on. A 25 ml zero-time sample is taken as a reference solution. One tablet is placed in the U.S.P. basket assembly, rotation is started, the assembly is immersed, and the timing is begun.

Samples of 10 ml are taken through a prewashed glass wool filter at 1, 2, 5, 10, 15, 30, 45, 60, 75, and 90 minutes. The optical absorbance is scanned directly on a suitable spectrophotometer from 400 to 250 nm, using the zero-time solution as the reference. The volume is not replaced; the deviations due to sample removal are negligible.

The absorption maximum at 295nm is used as the basis for calculation.

Dissolution rates were measured in triplicate for each formulation, and the averages are reported below in Table III.

TABLE III

Example	time (min)	Percent dissolved after									
		1	2	5	10	15	30	45	60	75	90
1		5	8	28	43	53	72	85			
2		8.5		34.5	51	62.5	82	90			
3		5		15	26	35	54	64.5			
4		2.5		8.5	15	22	39	52			
5		1	2	4	8	12	30	50	68	78	85
6		1	1.5	2	7	11	26	47	60	72	79

The same pattern of results is apparent for distribution rates as for disintegration times.

WHAT WE CLAIM IS:—

1. A medical tablet comprising a solid dispersion of Griseofulvin in polyethylene glycol and from 18 to 99% of the weight of the tablet of crosslinked polyvinylpolypyrrolidone (PVPP) as a disintegrating aid.

2. A tablet as claimed in Claim 1, comprising from 18 to 25% by weight of PVPP.

3. A tablet as claimed in Claim 2, comprising from 20 to 25% by weight of PVPP.

4. A tablet as claimed in any one of the preceding claims in which the PVPP is POLYCLAR AT.

5. A tablet as claimed in any one of the preceding claims in which the solid dispersion of Griseofulvin in polyethylene glycol contains from 2% to 50% by weight of Griseofulvin.

6. A tablet as claimed in Claim 5 in which the solid dispersion of Griseofulvin in polyethylene glycol contains from 20% to 30% by weight of Griseofulvin.

7. A tablet as claimed in any one of the preceding claims in which the polyethylene glycol has a molecular weight of from 4000 to 6000.

8. A medical tablet as described in Example 1 or Example 2.

9. A method for the production of a rapid disintegrating medicinal tablet comprising a solid dispersion of Griseofulvin in polyethylene glycol, characterised in that the said solid dispersion is formulated with cross-linked polyvinylpolypyrrolidone (PVPP) before formation of the tablet, the amount of PVPP being from 18 to 99% of the weight of the tablet.

10. A method as claimed in Claim 9, in which the amount of PVPP is from 18 to 25% of the weight of the tablet.

11. A method as claimed in Claim 10, in which the amount of PVPP is from 20 to 25% of the weight of the tablet.

12. A method as claimed in any one of Claims 9—11, in which the PVPP is POLYCLAR AT.

13. A method according to Claim 9, substantially as hereinbefore described.

14. A medicinal tablet comprising a solid dispersion of Griseofulvin in polyethylene glycol whenever prepared by a method as claimed in any one of Claims 9—13.

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